Delays in cancer care for children in low-income and middle-income countries: development of a composite vulnerability index

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Summary

Background Early access to diagnosis and care is essential to improve rates of survival from childhood cancer, particularly in low-income and middle-income countries (LMICs). Composite indices are increasingly used to compare country performance in many health fields. We aimed to develop a composite vulnerability index of risk of mortality associated with delays in care for childhood cancer in LMICs, and to compare the vulnerability index scores across countries.

Methods The composite vulnerability index was built in ten steps. A previous systematic review of determinants of delays in cancer care for children guided data selection. We collected exposure variables (determinants of delays in care) and outcome variables (childhood cancer-related mortality) from several large datasets. Data were analysed with regression models to identify determinants of delays in care that contribute to childhood cancer mortality. Significant indicators were aggregated into domains according to the socio-ecological model. We used geospatial tools to summarise and compare the composite vulnerability index scores across countries.

Findings We found that life expectancy, maternal education, fertility rate, availability of pathology services, bone marrow transplantation capacity, availability of treatment services (chemotherapy, radiotherapy, or surgery), number of pharmacists per 10 000 population, country income level, and out-of-pocket health expenditure were significantly associated with cancer mortality for children in LMICs. The highest levels of vulnerability were found in sub-Saharan Africa.

Interpretation Our composite vulnerability index can potentially serve as a valuable policy decision tool to help monitor country performance and guide interventions to reduce delays in care for children with cancer in LMICs.

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For the Chinese translation of the abstract see **Online** for appendix 1

For the Portuguese translation of the abstract see **Online** for appendix 2

For the Arabic translation of the abstract see **Online** for appendix 3

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For the Swahili translation of the abstract see **Online** for appendix 5

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Introduction

Globally, the burden of cancer in children remains high, particularly in low-income and middle-income countries (LMICs).[1] Recent estimates suggest that 85% of all paediatric cancer cases occur in LMICs.[2] Mortality from paediatric cancer in LMICs is disproportionately high, with nearly 80% of children with cancers dying in LMICs compared with 20% mortality in high-income countries.[3,4] Delays in cancer diagnosis and treatment are leading drivers of the high mortality in LMICs, with less than 30% of children in LMICs receiving timely cancer care. In this context, the WHO Global Initiative for Childhood Cancer has set a goal to decrease childhood cancer mortality to less than 60% worldwide by 2030.[1]

There are many drivers of high mortality for children with cancer in LMICs, but delays in diagnosis and care remain a leading underlying cause.[1] We previously conducted a systematic review to summarise the drivers of delays in childhood cancer care in LMICs.[5] Our findings suggested that cultural, socioeconomic, and demographic factors had the most substantial effect across the entire continuum of care. However, our review did not evaluate how these factors affect mortality from childhood cancer. An improved understanding of the association between the drivers of delays in care and deaths from cancer is essential to develop strategic interventions to improve cancer outcomes for children in LMICs.

Composite indices are often used to compare health outcomes between countries to inform policy makers of effective interventions, areas of need, and trends in regions or countries over time.[6] We aimed to develop a composite vulnerability index of delays in cancer care for children in LMICs and to use geospatial analysis to compare vulnerability indices across regions and countries. This composite vulnerability index could offer national governments, policy makers, and public health officials a tool to inform strategic interventions to decrease cancer mortality by reducing delays in childhood cancer care.

Methods

Study design

We followed the methodology described by the Organisation for Economic Co-operation and Development (OECD) to build our composite vulnerability index.[6] The

Research in context

Evidence before this study

In our previous systematic review, which evaluated determinants and risk factors of delays in childhood cancer care in low-income and middle-income countries (LMICs), we searched ten electronic databases and three websites for peer-reviewed studies and grey literature from inception. Search strings were built based on three constructs: (1) the population being children aged 0–18 years from LMICs; (2) the exposure being factors contributing to timely childhood cancer care; and (3) the outcome being delays in childhood cancer care, defined as any step across the entire childhood cancer continuum of care. No restrictions regarding language, publication date, outcome effect measure, study design, or study quality were applied. From 95 studies that pooled data from 39 636 participants across 97 LMICs, we identified 43 determinants and 24 risk factors that were associated with delayed childhood cancer care. Early access to diagnosis and care is essential to improve rates of survival from childhood cancer, particularly in LMICs where survival rates are less than 30% compared with 80% in high-income countries. Multiple lines of study suggest that health system capacity, economic development, and social factors are key drivers of early diagnosis and improved survival from cancer. However, how these factors collectively affect delays in care for cancer is poorly understood, limiting the ability of health system leaders to understand why some countries perform better than others. Composite indices are often used to compare health outcomes between countries to inform policy makers of effective interventions, areas of need, and trends in regions or countries over time.

Added value of this study

We found that life expectancy, maternal education, fertility rate, availability of pathology services, bone marrow transplantation capacity, availability of treatment services (chemotherapy, radiotherapy, or surgery), number of pharmacists per 10 000 population, country income level, and out-of-pocket health expenditure were significantly associated with cancer mortality in children in LMICs. The composite vulnerability index scores varied widely around the world, with the highest levels of vulnerability to mortality associated with delays in cancer care being in sub-Saharan Africa.

Implications of all the available evidence

The composite vulnerability index can potentially serve as a valuable policy decision tool to help monitor country performance and guide interventions to reduce delays and improve cancer outcomes for children in LMICs. Use of this index could allow health system leaders to compare national health systems to reduce cancer mortality and to follow national trends in improving timely cancer care.

OECD proposes ten steps to develop a composite index, starting with an appropriate theoretical framework. We followed this guideline in a sequential way: data were collected, assessed for missingness, analysed, normalised, weighted, and then aggregated to render appropriate comparison. Following these steps, validation of the index was confirmed through uncertainty and sensitivity analyses as well as evaluation of the coherence and correlation of the results with other well established, relevant indicators. The final step ensured the interpretability of the results through appropriate visualisation techniques. The ten steps proposed by the OECD and details on how each step was applied in this study are detailed in table 1.

See Online for appendix 6

Publicly available country-level data were used for this study. Therefore, no institutional review board approval was needed. Patient and public involvement was not feasible because of the nature of this review that assessed public and secondary data, and therefore patient and public involvement is not included in this study. No individually identifiable health information was assessed in this study.

Theoretical framework and data selection

We used findings from our previous systematic review as the theoretical framework to identify key determinants of delays in care for children with cancer in LMICs and aligned our methodology to the WHO CureAll framework as well as the socio-ecological model (SEM).[5,7,8] In brief, childhood cancer was defined as all-inclusive cancers according to the International Classification of Childhood Cancer, third edition.[9] Studies with a sample population older than 18 years or from high-income countries were excluded. Determinants and risk factors of delays in care were differentiated on the basis of whether they reported effect measures of association (risk ratio, odds ratio, hazard ratio, and adjusted prevalence ratio). Exposures reporting these measures of association were defined as risk factors. We found a total of 43 determinants and 24 risk factors that were associated with delays in cancer.

The 24 identified risk factors associated with delays in care were used to guide the selection of a set of proxy variables to be used in our composite index (appendix 6 pp 2–9). These proxy variables were collected for 134 LMICs from several public databases, including the 2019 Global Burden of Disease (GBD),[10] the World Bank dataset for 2019,[11] and the WHO Cancer Country Profiles 2020.[12] We also collected childhood cancer mortality data from the 2019 GBD. Country income level was based on the World Bank classification for 2019.[13] We compared the means for each variable across World Bank income classification (low-income country, lower-middle-income country, and upper-middle-income country) using χ^2 tests and analysis of variance ($p<0{\cdot}05$) when appropriate. Individual differences were identified by performing Tukey's studentised range analysis ($p<0{\cdot}05$).

	Rationale	Methodology
Theoretical framework	Provided the basis for the selection and combination of variables into a meaningful composite indicator	We performed a systematic review of the literature to identify risk factors and determinants of delayed care for childhood cancer in LMICs. Ten databases and additional organisation websites were searched to ensure comprehensiveness. We included grey literature to avoid publication bias.
Data selection	Facilitated analytical soundness, measurability, and relevance of the indicators to the phenomenon being measured	Proxy variables were selected on the basis of results of the systematic review (appendix 6 pp 2–9). Only risk factors that reported effect measures of association were used. Data sources were World Bank datasets, WHO Cancer Country Profiles 2020, and Global Burden of Disease 2019.
Imputation of missing data	Was needed to provide a complete dataset for index building and cross-country comparison	A missing-at-random pattern was identified in the data. Overall, 6% of data were missing in our dataset. 17 (49%) of 35 variables had missing data, ranging from 0·75% to 31·34% (appendix 6 p 10). Countries were only excluded when outcome data were missing; however, missingness of exposure data was not a factor for exclusion. 134 (99%) of 135 countries were included in this study (appendix 6 p 12). Multiple imputation of chain equations was performed with the MICE package in R. To ensure accuracy, the number of multiple imputations was set at 100 and the number of iterations was set at 30 (appendix 6 p 14). Predictive mean matching was used for numeric variables, logistic regression was used for categorical variables with two levels, and polytomous regression was used for categorical variables with more than two levels. Rubin's Rules were applied to pool parameter estimates in the simple and multiple regression models.
Multivariate analysis	Used to study the overall structure of the dataset, assess its suitability, and guide subsequent methodological choices	We chose to perform regression analyses over other multivariate analyses (ie, principal component analysis) to ensure interpretability of results over flexibility. Statistically significant variables at p<0·10 from simple linear regression models were included in the multiple regression model. Statistically significant variables at p<0·10 and variables on the limit p=0·10 from the final full model were included as indicators in the vulnerability index. Directionality of the coefficient was interpreted from the simple linear regressions as we believe these one-to-one relationships better characterised the individual relationship between exposure and outcome. For instance, we interpreted that higher density of pharmacists is more likely associated with a decrease in cancer mortality rates.
Normalisation	Carried out to render the variables comparable	Continuous variables were standardised in the full model to facilitate comparison; however, our index also included categorical variables, for which standardisation was not possible
Weighting and aggregation	Method of grouping the selected variables that respect both the theoretical framework and the data properties	The index indicators were grouped into domains according to the four levels of the socio-ecological model: individual (domain 1); interpersonal and family (domain 2); community and organisation (domain 3); and policy and environment (domain 4).
Uncertainty and sensitivity analysis	Undertaken to assess the robustness of the composite indicator	Sensitivity analysis was done with an approach of p value thresholds to ensure inclusivity and flexibility (appendix 6 p 15). p values at <0·05, <0·10, and <0·20 were used for model comparison in the validation step.
Back to the data	Was needed to show the main drivers for an overall good or bad performance	We built a choropleth index table to facilitate country comparison at every level (indicator, domain, and overall; appendix 6 p 16).
Links to other indicators	Made to correlate the composite indicator (or its dimensions) with existing (simple or composite) indicators as well as to identify linkages through regressions	The overall and domain indexes were correlated to the other two composite indicators pertinent to the scope of this study (appendix 6 p 21): health-care access and quality index and universal health coverage index.
Visualisation of the results	Visualisation can influence or enhance the interpretability of results	Country-level results were displayed in choropleth maps. Hot-spot analysis was applied to visualise statistically significant clusters of vulnerability.

This table was modified from the original source available at the *OECD Handbook on Constructing Composite Indicators: Methodology and User Guide.*[6] MICE=Multivariate Imputation by Chained Equations. OECD=Organisation for Economic Co-operation and Development.

Table 1: **Ten steps followed to build the composite vulnerability index**

Multivariate analysis

The proxy variables were used as exposure variables to evaluate their association with cancer mortality in children using simple and multiple linear regression models. Simple regression models were built for each variable. Only variables with a p value less than 0·10 were included in the multiple regression model. We then did a backward variable elimination process based on p value and model fitting. Variables were removed from the multiple regression model one by one, starting from the variables with the highest p values until reaching the best adjusted R^2 for the model. Next, we assessed multicollinearity through variation inflation factor (VIF) analysis. Variables with VIFs greater than 20 were removed from the final model one by one, starting from the variables with the highest VIFs. In the final model, statistical significance level was set at a p value less than 0·10. Significant exposure variables and variables at the limit p=0·10 from the final multiple regression model were included as indicators in the composite vulnerability index. In this way, we ensured our final set of indicators had maximum flexibility and inclusivity to account for limitations intrinsic to the ecological design. All statistical analyses were generated using RStudio (version 4.2.2). We assessed the quality of our composite index using the quality analysis framework as described in the OECD guide (appendix 6 p 22).[6]

Weighting and aggregation

The indicators identified as statistically significant in the final multiple regression model were aggregated into domains according to the levels of the SEM (individual, interpersonal and family, community and organisation, and policy and environment) to offer a comprehensive view of the domains of delays in care that independently affect childhood mortality in LMICs. No distinction of weight was applied to the index indicators before aggregation because of the existence of both categorical

	Total countries (n=134)	Income level			p value
		Low-income country (n=29)	Lower-middle-income country (n=50)	Upper-middle-income country (n=55)	
Risk factor variables					
Individual domain					
HIV prevalence at age 0–14 years, %	134 (100%)	0·02 (0·04)	0·02 (0·05)	0·01 (0·00)	0·15
HIV death rate at age <5 years per 1000 livebirths	134 (100%)	0·00 (0·00)	0·00 (0·00)	0·00 (0·00)	0·11
Life expectancy at birth, total years	129 (96%)	62·90 (5·00)	68·50 (5·62)	73·77 (0·60)	<0·0001
Interpersonal and family domain					
Education years per capita	134 (100%)	5·62 (2·27)	7·64 (2·28)	9·90 (0·22)	<0·0001
Maternal education 0 years, %	134 (100%)	34·24 (21·34)	15·46 (14·12)	3·06 (0·56)	<0·0001
Maternal education >6 years, %	134 (100%)	52·16 (23·68)	75·51 (18·41)	93·72 (0·93)	<0·0001
Maternal education >12 years, %	134 (100%)	15·36 (14·62)	30·15 (19·94)	51·05 (2·38)	<0·0001
Maternal education >15 years, %	134 (100%)	4·09 (5·30)	9·46 (9·38)	16·96 (1·32)	<0·0001
Total fertility rate	134 (100%)	4·46 (1·29)	3·02 (0·96)	2·06 (0·07)	<0·0001
Community and organisations domain					
Health access and quality, index	134 (100%)	31·58 (11·02)	45·08 (13·13)	61·67 (1·61)	<0·0001
Hospital beds per 1000 population	134 (100%)	1·32 (2·41)	1·90 (1·70)	2·99 (0·27)	<0·0001
Nurses and midwives per capita	134 (100%)	11·28 (8·61)	19·39 (16·87)	37·68 (3·18)	<0·0001
Pharmacists per 10 000 population	134 (100%)	1·48 (0·87)	3·10 (2·55)	5·92 (0·56)	<0·0001
Physicians per 10 000 population	134 (100%)	3·09 (4·61)	7·82 (9·21)	16·36 (1·97)	<0·0001
Rural population as proportion of total population, %	133 (99%)	63·93 (14·08)	53·53 (18·00)	35·52 (2·45)	<0·0001
Number of external beam radiotherapy per 10 000 patients with cancer	123 (92%)	0·54 (0·90)	3·43 (3·82)	7·50 (0·65)	<0·0001
Number of CT scanners per 10 000 patients with cancer	118 (88%)	12·49 (15·39)	25·65 (23·57)	53·62 (5·85)	<0·0001
Number of MRI scanners per 10 000 patients with cancer	117 (87%)	4·37 (7·54)	7·97 (8·40)	21·97 (2·75)	<0·0001
Number of PET or PET–CT scanners	120 (90%)	0·03 (0·17)	0·78 (2·36)	1·39 (0·27)	0·012
Number of public cancer centres per 10 000 patients with cancer	92 (69%)	4·25 (6·79)	6·14 (11·69)	6·72 (1·30)	0·70
Number of surgeons per 10 000 patients with cancer	93 (69%)	159·36 (490·86)	382·68 (582·16)	730·91 (111·50)	0·0018
Number of nuclear medicine physicians per 10 000 patients with cancer	109 (81%)	0·78 (1·40)	3·90 (6·94)	11·40 (2·73)	0·0012
Availability of population-based cancer registry	105 (78%)	18 (17%)	40 (38%)	47 (45%)	0·87
Registration activity	32 (30%)	6 (33%)	11 (28%)	15 (32%)	..
Population-based cancer registry	73 (70%)	12 (67%)	29 (73%)	32 (68%)	..
Early detection programme for childhood cancer	118 (88%)	27 (23%)	44 (37%)	47 (40%)	0·049
Yes	23 (20%)	2 (7%)	7 (16%)	14 (30%)	..
No	95 (81%)	25 (93%)	37 (84%)	33 (70%)	..
Availability of pathology services	132 (99%)	29 (22%)	49 (37%)	54 (41%)	<0·0001
Generally available	96 (73%)	11 (38%)	35 (71%)	50 (93%)	..
Generally not available	36 (27%)	18 (62%)	14 (29%)	4 (7%)	..
Bone marrow transplantation capacity	114 (85%)	25 (22%)	46 (40%)	43 (38%)	0·0078
Generally available	19 (17%)	1 (4%)	5 (11%)	13 (30%)	..
Generally not available	95 (83%)	24 (96%)	41 (89%)	30 (70%)	..
Palliative care availability: community or home-based care	129 (96%)	28 (22%)	49 (38%)	52 (40%)	0·0033
Generally available	30 (23%)	3 (11%)	7 (14%)	20 (38%)	..
Generally not available	99 (77%)	25 (89%)	42 (86%)	32 (62%)	..

(Table 2 continues on next page)

and numerical data. Thus, standardisation of all variables was not appropriate. Ranking of vulnerability was done within each indicator, within each domain, and overall. For continuous data and on the basis of every indicator, each country was sorted (ascending or descending) and assigned a score from 0 to 1 (less vulnerable to more vulnerable) by performing a percentage ranking. For categorical data, variables with two levels, generally

	Total countries (n=134)	Income level			p value
		Low-income country (n=29)	Lower-middle-income country (n=50)	Upper-middle-income country (n=55)	
(Continued from previous page)					
Defined referral system	114 (85%)	24 (21%)	42 (37%)	48 (42%)	0·0050
Yes	33 (29%)	2 (8%)	10 (24%)	21 (44%)	..
No	81 (71%)	22 (92%)	32 (76%)	27 (56%)	..
Number of treatment services (surgery, chemotherapy, and radiotherapy)	132 (99%)	29 (22%)	49 (37%)	54 (41%)	<0·0001
None	37 (28%)	18 (62%)	14 (29%)	5 (9%)	..
One and two	33 (25%)	7 (24%)	12 (24%)	14 (26%)	..
Three	62 (47%)	4 (14%)	23 (47%)	35 (65%)	..
Policy and environment domain					
Universal health coverage, index	134 (100%)	43·25 (10·04)	55·34 (10·53)	68·05 (9·37)	<0·0001
Out-of-pocket fraction of total health expenditure, %	134 (100%)	42·54 (19·49)	39·34 (19·78)	33·36 (19·67)	0·10
Gross domestic product, US$	134 (100%)	1780·34 (1442·44)	5211·53 (2807·96)	12799·74 (4847·38)	<0·0001
Gross national income, US$	120 (90%)	692·17 (229·92)	2443·33 (971·85)	7157·96 (2201·68)	<0·0001
Outcome variables					
Cancer mortality frequency	134 (100%)	678·95 (776·67)	920·29 (2259·17)	502·42 (1582·58)	0·48
Cancer mortality per 100 000 population	134 (100%)	6·75 (2·34)	5·20 (1·93)	4·65 (1·41)	<0·0001

Data are n (%) or mean (SD). *Comparison of means was performed with analysis of variance. Statistically significant different means at p<0·05 were obtained by performing the Tukey's studentised range.

Table 2: **Comparison of the risk factors for delays in cancer care for children and outcome variables by World Bank income level among countries**

available and generally not available, were given the scores of 0·7 and 0·3, respectively. Categorical variables with three levels (eg, income: low-income country, lower-middle-income country, and upper-middle-income country) were given the scores of 0·0, 0·50, and 1·0, in a logical ascending order. The partial scores from each indicator were added to obtain each domain vulnerability by sorting and calculating the percentage rank. Finally, partial scores from each domain were added to obtain an overall vulnerability score for each country. The overall vulnerability scores were sorted and ranked. This methodology was previously used to calculate vulnerability scores for numerical variables in other indexes.[14]

Visualisation of results

In the final step, we used several geospatial analysis tools to graphically summarise the vulnerability index scores. First, we displayed the overall vulnerability index scores across countries worldwide using a choropleth map. Second, we identified clusters of high and low vulnerability with hot-spot analysis (Getis-Ord Gi*). This machine-learning technique was used to identify geographical clusters of high vulnerability. The highest vulnerability scores and lowest vulnerability scores were calculated with 90%, 95%, and 99% statistical significance. The distance band to define neighbouring features was set as the contiguity of edges and corners among countries. Geospatial analyses were generated using ArcMap 10.3 (ESRI, Redlands, CA, USA).

Role of the funding source

There was no funding source for this study.

Results

Our analysis allowed the creation of a composite vulnerability index of delays in cancer care for children. On the basis of the 24 risk factors found in our previous systematic review, we selected 34 proxy variables associated with delays in care in LMICs (appendix 6 p 2). These variables were organised according to the underpinnings of the CureAll framework and the SEM. Most proxy variables were found for the community and organisation level, which mainly depicted the health system infrastructure. By contrast, the individual level had the least number of proxy variables. Endogenous variables, such as beliefs and misconception, were not matched with a proxy variable. All pillars and enablers of the CureAll framework were distributed across proxy variables and domains of the SEM.

134 LMICs were included in the analysis, including 29 (22%) low-income countries, 50 (37%) lower-middle-income countries, and 55 (41%) upper-middle-income countries (table 2). The comparison analyses suggested that 28 (85%) of the 33 exposure variables were different across income classification (all p<0·5; table 2). Rural population, total fertility rate, and maternal education of 0 years were inversely associated with income level. By contrast, maternal education of more than 6 years, more than 12 years, and more than 15 years, level of education

	Simple regression model			Standardised multiple linear regression*		
	Parameter estimate	SE	p value	Parameter estimate	SE	p value
Individual domain						
HIV prevalence at age 0–14 years, %	−0·73	0·85	0·39	..	..	..
HIV death rate at age <5 years per 1000 livebirths	−24·58	117·47	0·84	..	..	..
Life expectancy at birth, total years	−0·01	0·00	0·0049	0·12	0·06	0·040
Interpersonal and family domain						
Education years per capita	−0·05	0·01	<0·0001	..	..	..
Maternal education 0 years, %	0·01	0·00	<0·0001	−0·34	0·11	0·0015
Maternal education >6 years, %	−0·01	0·00	<0·0001	−0·40	0·11	0·0006
Maternal education >12 years, %	−0·01	0·00	<0·0001	..	..	..
Maternal education >15 years, %	−0·01	0·00	0·0037	..	..	..
Total fertility rate	0·11	0·02	<0·0001	0·09	0·06	0·11
Community and organisation domain						
Health access and quality, index	−0·01	0·00	<0·0001	..	..	..
Hospital beds per 1000 population	−0·03	0·01	0·042	..	..	..
Nurses and midwives per capita	−0·00	0·00	0·44	..	..	..
Pharmacists per 10 000 population	−0·02	0·01	0·017	0·06	0·04	0·086
Physicians per 10 000 population	−0·00	0·00	0·78	..	..	..
Rural population as proportion of total population, %	0·00	0·00	0·0066	−0·04	0·04	0·30
Number of external beam radiotherapy per 10 000 patients with cancer	−0·02	0·01	0·0009	−0·05	0·04	0·19
Number of CT scanners per 10 000 patients with cancer	−0·00	0·00	0·010	..	..	..
Number of MRI scanners per 10 000 patients with cancer	−0·00	0·00	0·039	..	..	..
Number of PET or PET–CT scanners	−0·03	0·02	0·11	..	..	..
Number of public cancer centres per 10 000 patients with cancer	−0·00	0·00	0·19	..	..	..
Number of surgeons per 10 000 patients with cancer	−0·00	0·00	0·64	..	..	..
Number of nuclear medicine physicians per 10 000 patients with cancer	−0·01	0·00	0·0084	..	..	..
Availability of population-based cancer registry (reference=population-based cancer registry)						
Registration activity	0·06	0·07	0·43	..	..	..
Early detection programme for childhood cancer (reference=yes)						
No	0·05	0·08	0·47	..	..	..
Availability of pathology services (reference=generally available)						
Generally not available	0·23	0·07	0·0005	0·16	0·09	0·076
Bone marrow transplantation (reference=generally available)						
Generally not available	0·26	0·08	0·0021	0·18	0·09	0·044
Palliative care availability (reference=generally available)						
Generally not available	0·16	0·07	0·028	..	..	..
Defined referral system (reference=yes)						
No	−0·02	0·07	0·81	..	..	..
Number of treatment services (reference=zero)						
One and two	−0·06	0·08	0·45	0·15	0·10	0·12
Three	−0·21	0·07	0·0047	0·20	0·11	0·072

(Table 3 continues on next page)

in years, gross domestic product, health access and quality, universal health coverage, health-care workforce variables, health-care infrastructure variables, and gross national income were directly associated with income level. Maternal education of 0 years, maternal education more than 6 years, health-care workforce variables, health-care infrastructure variables, gross domestic product, and gross national income showed the greatest gaps of difference across income levels.

From the linear regression models, we found that 24 (73%) exposure variables were directly associated with cancer mortality (all $p<0·05$; table 3). Variables that were not associated with childhood cancer mortality in the univariate models were HIV prevalence, HIV mortality in

	Simple regression model			Standardised multiple linear regression*		
	Parameter estimate	SE	p value	Parameter estimate	SE	p value
(Continued from previous page)						
Policy and environment domain						
Universal health coverage	–0·01	0·00	<0·0001	–0·11	0·07	0·15
Out-of-pocket fraction of total health expenditure	0·00	0·00	0·0023	0·06	0·03	0·027
Gross domestic product, US$	–0·00	0·00	<0·0001	..	..	..
Gross national income, US$	–0·00	0·00	<0·0001	..	..	..
Country income (reference=low income)						
Lower-middle income	–0·27	0·08	0·0005	–0·14	0·09	0·096
Upper-middle income	–0·36	0·08	<0·0001	–0·07	0·12	0·57

Imputed data were used in this analysis. Statistically significant values were calculated at p<0·10. Indicators selected to build the vulnerability index were life expectancy at birth, maternal education of 0 years, maternal education of less than 6 years, total fertility rate, number of pharmacists per 10 000 population, availability of pathology services, bone marrow transplantation, number of treatment services, and out-of-pocket fraction of total health expenditure. *Proxy exposure variables eliminated during variance inflation factor analysis were not included in this full model.

Table 3: **Linear regression models of the association between the risk factors of delayed childhood cancer care and childhood cancer mortality in low-income and middle-income countries**

children younger than 5 years, nurses and midwives per capita, physicians per capita, density of PET or PET–CT scanners, density of public cancer centres, density of surgeons, availability of population-based cancer registry, existence of early detection programme, and existence of defined referral systems (table 3).

Life expectancy at birth, maternal education of 0 years, maternal education of more than 6 years, bone marrow transplantation capacity, and out-of-pocket fraction of total health expenditure had p values less than 0·05 in our final model (table 3). The number of treatment services (surgery, chemotherapy, and radiotherapy), availability of pathology services, pharmacists per 10 000 population, and country income level were statistically significant with p values less than 0·10 in our final model. Total fertility rate showed a p value of 0·11 in our model. Life expectancy, maternal education of 0 years, maternal education of more than 6 years, bone marrow transplantation availability, number of treatment services (surgery, chemotherapy, and radiotherapy), availability of pathology services, pharmacists per 10 000 population, and country income level were directly associated with mortality. By contrast, out-of-pocket fraction of total health expenditure and total fertility rate were indirectly associated with mortality. We included these ten variables as indicators in our composite vulnerability index.

The overall vulnerability index score varied widely around the world, with spatial distribution showing disparities among regions and countries (figure 1A). Most African countries had highly vulnerable scores, with most countries being ranked higher than the 70th percentile. The five countries with the highest vulnerability index scores were Cameroon (score 1·000), Angola (0·992), Mauritania (0·985), Senegal (0·977), and Nigeria (0·970). The five countries with the lowest vulnerability index scores were Lebanon (score 0·000), Federated States of Micronesia (0·008), Cuba (0·015), Thailand (0·015), and Viet Nam (0·030). Vulnerability scores for all countries are available in appendix 6 (p 16). These findings were supported by geospatial hot-spot analysis, which identified the most crucial geographical cluster of vulnerability in sub-Saharan Africa (figure 1B). The overall vulnerability index and all four domain indexes showed moderate to high correlation with the Healthcare Access and Quality[15] and Universal Health Coverage[16] indexes (appendix 6 p 21).

Discussion

We developed a novel composite vulnerability index to summarise the effect of the drivers of delays in care on childhood cancer mortality in LMICs. We also identified crucial indicators of action that directly affect cancer outcomes and are aligned with the WHO Global Initiative for Childhood Cancer CureAll framework, the currency of communication in global childhood cancer.[8] Sub-Saharan Africa was identified as the most vulnerable region for childhood cancer mortality associated with delays in care.

Public health officials often use composite vulnerability indexes to identify at-risk populations during disasters or health emergencies, compare country performance in a given health field, or track changes in performance over time.[14,17] As shown in other diseases, vulnerability is a dynamic concept—a person or a group might not be vulnerable to cancer mortality at one time, but could subsequently become vulnerable depending on the context of their health system, access to care, and other variables. The inclusion of demographic and population health indicators (fertility and life expectancy), social indicators (maternal education), health infrastructure indicators (availability of pathology services, availability of treatment services, bone marrow transplantation capacity, and

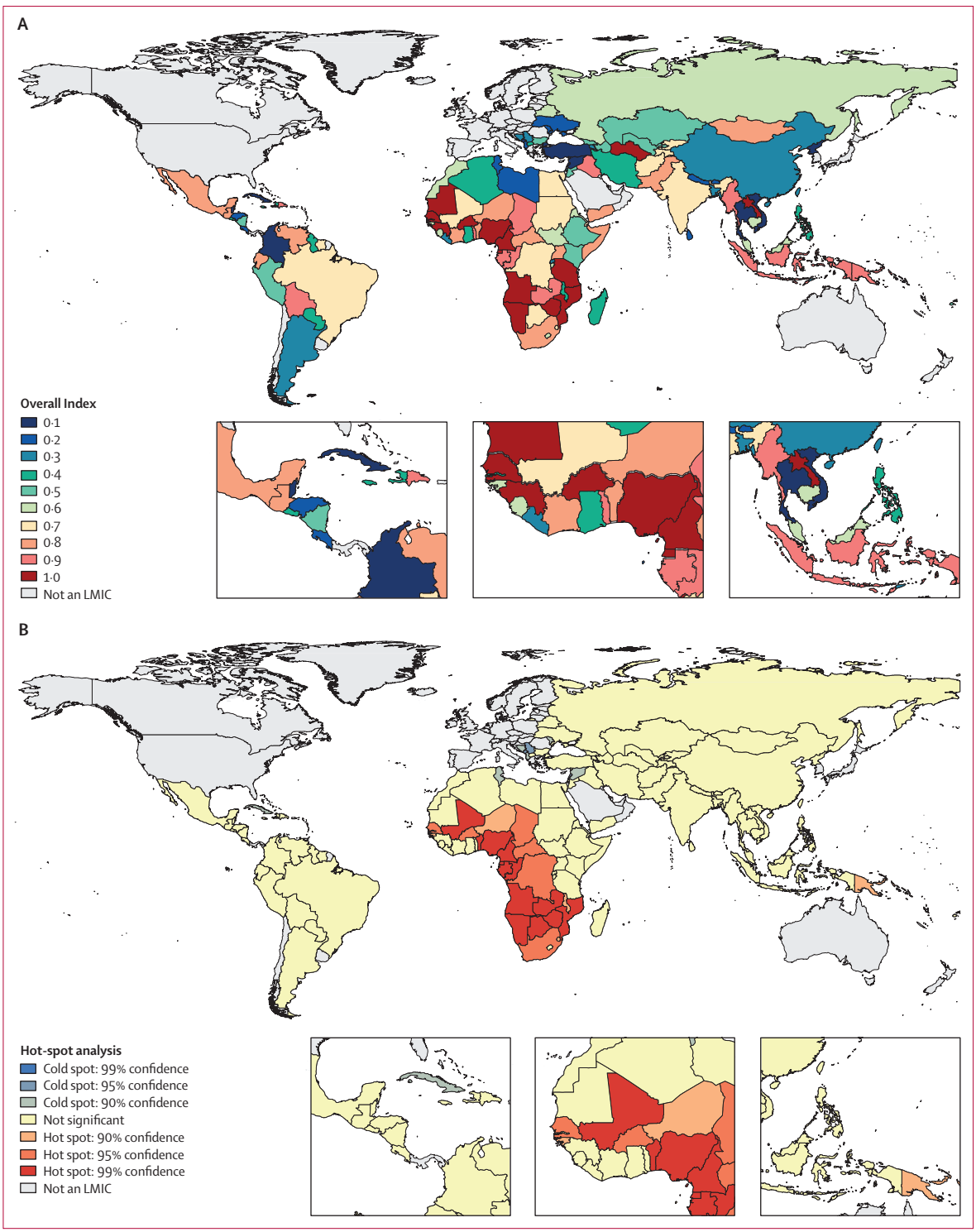

Figure 1: **Vulnerability index score map and hot-spot analysis of risk factors of delayed childhood cancer care associated with childhood cancer mortality in LMICs**

(A) Vulnerability index score map. The index scores are reported in decile intervals and quantify the risk of experiencing delays in childhood cancer care that directly influence mortality. Higher scores indicate higher vulnerability. (B) Geospatial hot-spot analysis map. In panel B, hot spots indicate clusters of countries with high vulnerability scores surrounded by neighbouring countries with high vulnerability scores. Cold spots indicate clusters of countries with low vulnerability scores surrounded by neighbouring countries with low vulnerability scores. LMIC=low-income and middle-income country.

pharmacist density), and financing indicators (out-of-pocket expenditure and country income level) makes our index a holistic and balanced policy decision tool that addresses the complex social, medical, economic, and structural drivers of delays in childhood cancer care. From a policy standpoint, our goal was to develop an accessible and holistic tool to quantify the direct effect of the drivers of delays in care on mortality and thereby allow health-care leaders to assess childhood cancer systems, compare country performance, and track progress over time. To achieve this goal, we included not only variables related to cancer systems such as access to diagnostic and treatment resources, but also broad development and social variables that have a substantial effect on access to timely care. For instance, travel distance and scarcity of reliable transportation are among the most common causes for delays in cancer care. These are not directly related to cancer care per se, but help to understand why patients present at late stages of the disease. Unfortunately, there are no nationwide data for this kind of complex variable. Therefore, we used a proxy variable: rurality.

The importance of maternal education as a determinant of childhood mortality in other childhood conditions has been well documented, although the effect of maternal education on delays in cancer care for children remains poorly understood. A meta-analysis suggested a causal link between maternal education and all-cause childhood mortality in LMICs.[18] In terms of cancer care, Isaevska and colleagues[19] reported a direct association between maternal education and childhood cancer survival, especially for children with central nervous system tumours, who frequently require long-term treatment and special care. We found that maternal education was a more important predictor of cancer mortality than parental education (both parents). Aslam and Kingdon[20] reported similar results for general child health outcomes in Pakistan and suggested that this phenomenon might be explained by the pivotal role that mothers usually have as primary caregivers. Our findings suggest that improving access to maternal education might improve outcomes and reduce delays in care for children with cancer. Interventions should be oriented to promote basic health-related knowledge in mothers through community health workers, especially in rural areas.

Our findings also suggest that several measures of cancer-related health system capacity are important determinants of delays in cancer care for children. Access to diagnostic and treatment services, as well as adequate human resources, are essential to achieve quality health care and universal health coverage.[21,22] However, capacity building for cancer systems for children is frequently underfunded in national health budgets. Health expenditure for cancer care in LMICs is only 6·2% of the global cancer expenditures, despite the high global burden of cancer in LMICs.[23] In this context, families are often at risk of experiencing catastrophic health expenditure and impoverishing expenditure due to substantial out-of-pocket expenses to access cancer diagnosis and treatment for their children.[8] Consequently, children are left undiagnosed, experience delays throughout the continuum of care, or abandon treatment. Our data suggest that increasing access to diagnostic and treatment capacity is a necessary step towards decreasing childhood cancer mortality in LMICs. Therefore, future initiatives should include the allocation of comprehensive cancer care packages within universal health coverage schemes.

Individually, each risk factor identified plays a role in delays in cancer care and outcomes. However, it is the interplay of these risk factors that strongly affects a country's vulnerability to mortality associated with delays in care. For example, some countries, such as Dominican Republic, Ecuador, and Mexico, have a high life expectancy score (indicating a low vulnerability) but a high overall vulnerability score driven by poor health system factors or policy financing, not by individual or interpersonal or family factors. At the other end of the spectrum, Rwanda (vulnerability index score 0·226) had one of the lowest overall vulnerability scores, driven in large part by strong health system infrastructure and policy financing scores, along with good or marginal life expectancy and maternal education scores. Rwanda has set an example of supporting children's care in LMICs by building strong referral networks and lowering expenses for treatment.[24,25] These findings suggest that improving children's cancer care in LMICs is multifaceted and largely driven by health system factors, as well as country-level and social factors. Some risk factors, such as life expectancy, are not easily modifiable and must be interpreted as part of the overall trajectory of a country's readiness in providing children's cancer care.

By providing a policy tool to help countries monitor their progress in reducing vulnerability to cancer mortality, our study could contribute to the momentum created when WHO set the goal of improving childhood survival rates to at least 60% worldwide by 2030.[1] Our index is well aligned with the CureAll framework, allowing policy makers to track their progress in improving cancer care for children when addressing the roots of delayed care (figure 2). The CureAll framework is a shared operational and integrated child-centred and family-centred approach with specific strategies and priority actions to achieve the forementioned goal by increasing capacity and quality of childhood cancer systems worldwide.[8] Our index relates to all CureAll pillars and enablers, and advocates for the inclusion of additional metrics to measure progress on individual and interpersonal indicators (ie, proportion of outreach campaigns targeted to caregivers and proportion of funded benefit packages to support for families with several children). Our index also directly responds to eight of the ten CureAll core projects by analysing and providing a tool for monitoring and evaluation of childhood cancer systems in the context of delays in care. We also identify priority areas to leverage advocacy,

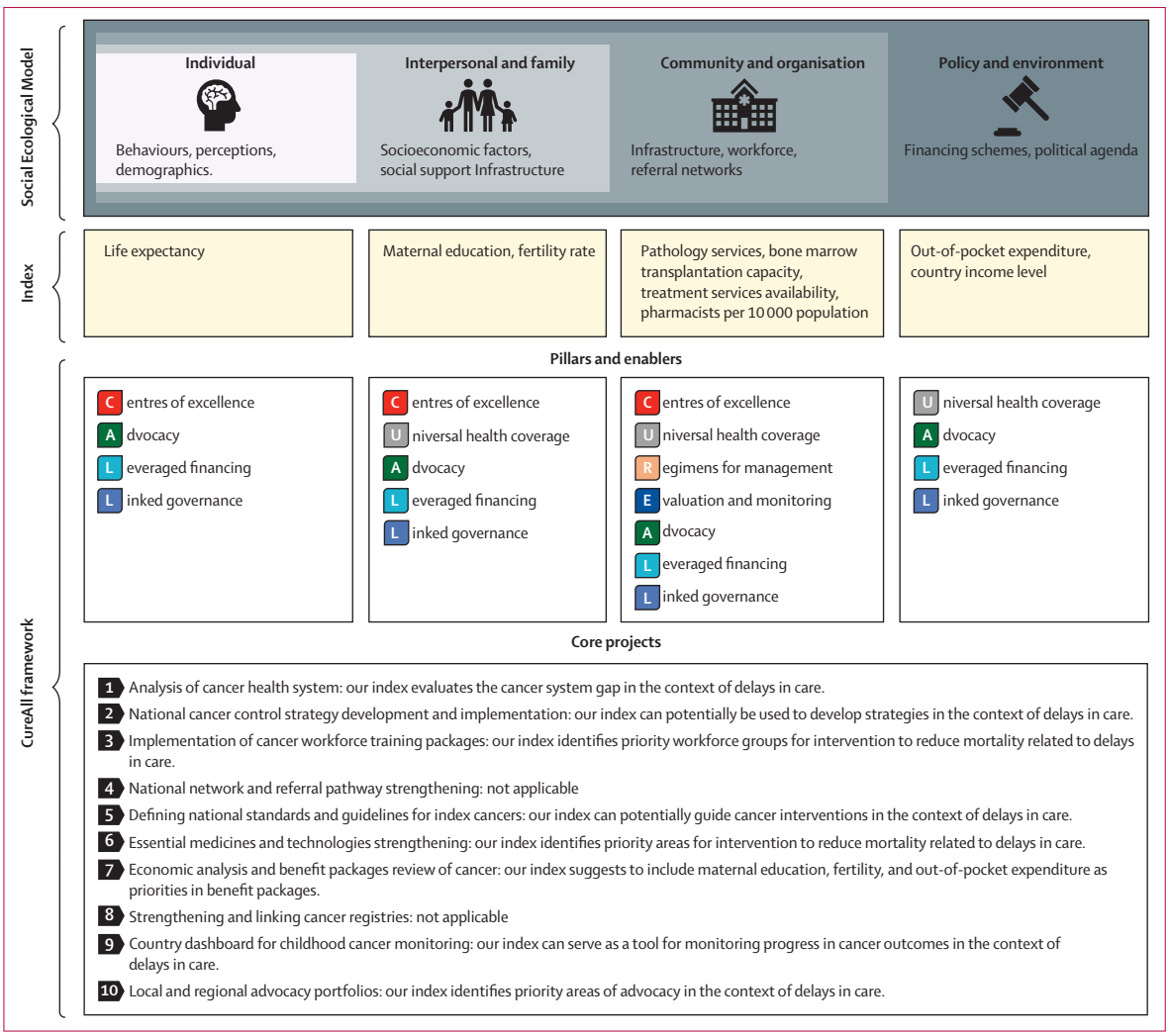

Figure 2: **Alignment of the composite vulnerability index with the CureAll framework**

financing, and governance with substantial effect on cancer outcomes.

Furthermore, our index can potentially serve as a tool to monitor progress of LMICs as a whole and within subregions. It can be used as a substitute for a national or local index for which collecting data to develop a tailored index is still a challenge, or it can serve as a template tool towards the development of locally tailored indexes. This policy tool is a flexible and inclusive way to convey the priority areas of action, since our base framework was developed with a good representation of nationalities, paediatric ages, and cancer diagnoses. Although this study did not aim to compare our index with other well established and robust indexes used to monitor and evaluate affordable and high quality access to health care worldwide, the correlation between our index and the Health Access Quality and Universal Health Coverage indexes point to the robustness and applicability of our findings.[15,16]

Our study has several limitations. First, scarce proxy national-level data were available to measure all factors of delays in care for childhood cancer. Therefore, important variables such as families' or providers' cancer knowledge were not assessed due to scarcity of data at a national level. Additionally, this study only accounts for the exogenous (observable) variables related to delayed childhood cancer care. Endogenous (unobservable) variables such as beliefs and attitudes were not included because of the absence of data. Second, we found an overall 6% of missing data, with up to 31% of missing data for some variables. We addressed this issue by performing multiple imputation of the data. However, there is always a small risk of bias in using imputed data. Third, an ecological fallacy often exists when developing composite indexes related to the underlying model and study design, risking inaccurate conclusions of cause-and-effect relationships; therefore, the results of this study should be interpreted with caution.[26] We have tried to overcome this limitation by including only exposure

variables that were guided by a determinant of delays in care that have appropriate measures of association (risk ratio, odds ratio, hazard ratio, and adjusted prevalence ratio).[27] Finally, our index was created under the premise that childhood cancer care is unique compared with cancer in adults, and that children in LMICs experience unique challenges compared with children in high-income countries.[1] Therefore, this index cannot be generalised to adult and high-income-country populations.

We have described a data-driven composite vulnerability index to monitor delays in childhood cancer care and guide interventions to improve survival rates for children with cancer. This index could serve as a starting point to improve understanding of delays in care for childhood cancer along the entire continuum of care. We encourage national governments and other stakeholders to use this policy tool according to their unique context and access to high-quality data.

Contributors

CC-C conceived and designed the study, collected and analysed the data, produced the visualisations, and drafted the original manuscript. ST, HeER, and ERS contributed to the study design. ERS and HeER supervised the project. ERS and CC-C were the data curators and directly accessed and verified the underlying data in this study. HaER, KS, CS, and EM contributed with critical input and revision to the manuscript. All authors had access to all the data, contributed to the interpretation of the data, and revised, edited, and approved the final version of the manuscript before submission. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data used in this study are publicly available and have been cited in detail in appendix 6.

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